

Infertility, Andrology and the Testis

155

A 5-year review of modern methods of sperm retrieval in the presence of inoperable obstructive azoospermia

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Objective: To present and assess the efficacy of new approaches for the treatment of infertility due to inoperable obstructive azoospermia in a prospective study during 1991–1996.

Patients and methods: Thirty-seven couples (all female partners aged \leq 40 years) presenting with infertility secondary to obstructive azoospermia (congenital absence of vasa, congenital vasal atresia and failed epididymo-vasostomy) were studied. Female partners were superovulated using human menopausal gonadotrophin after a standard long protocol of pituitary down-regulation. Oocytes were retrieved by ultrasound-guided transvaginal aspiration. A microsurgical epididymal sperm aspiration procedure (MESA) was performed. In the first group of 20 couples treated successively, this was followed by conventional IVF; in the second group of 17 couples, MESA was followed by IVF and assisted fertilization with intracytoplasmic sperm injection (ICSI).

Results: MESA + conventional IVF resulted in a fertilization rate of 17% with no pregnancies. In contrast, MESA + ICSI resulted in a fertilization rate of 59.7% and a pregnancy rate of 29.4%.

Conclusion: This study shows the combination procedure of MESA + ICSI to be much more efficient than MESA + conventional IVF and is the effective procedure of choice as treatment for 'inoperable' obstructive azoospermia. The technical and ethical issues relating to these modern treatments for fertility will be fully discussed.

156

PESA with ICSI: simplified sperm retrieval and microinjection in patients with azoospermia

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Introduction: To evaluate the recovery rate of spermatozoa from the epididymis using a percutaneous aspiration technique (PESA) and to assess the fertilization rate after intracytoplasmic sperm injection (ICSI), and pregnancy potential.

Patients and methods: Seventy-nine patients with obstructive (65) and secretory (14) azoospermia underwent a total of 90 treatment cycles of IVF with ICSI. In these patients, sperm aspiration was achieved by directing a 21–23 G butterfly needle connected to a syringe into either the head or corpus of the epididymis after identification by palpation. The aspirate was then washed out of the needle and tubing into a sterile Eppendorf tube using IVF culture medium. If repeated attempts to retrieve sperm by PESA proved unsuccessful, testicular sperm aspiration/biopsy was performed (15).

Results: The mean age of the female patients treated with PESA and ICSI was 34.2 years. The number of oocytes collected, injected, fertilized and cleaved, and the number of cycles with embryo transfer together with the outcome are shown in the Table.

No. patients /cycles	No. oocytes collected	No. MII injected	No. 2PN (%)	No. cleaved (%)	No. embryo transfers (%)	No. clinical* pregnancy (%)
79/90	1135	845	451 (53.4)	395 (87.8)	85 (94.4)	27 (31.7/ET)

* (11 \times delivered, 13 \times ongoing, 3 \times late miscarriage)

The total number of embryos transferred was 233. The maximum number of embryos replaced per cycle was limited to three. A further 56 embryos were suitable for cryopreservation. Failure of fertilization occurred in two cycles, and in three more cycles the embryos did not cleave. In 12 of the 15 cycles in which PESA failed to yield sperm, testicular spermatozoa were used, giving a 14.2% retrieval failure rate.

Discussion: PESA can be used successfully to retrieve sperm in men with azoospermia due to obstructive or non-obstructive disorders. The technique was simple, cost-effective and practically free of complications compared to an open micro-surgical procedure (i.e. MESA). Should PESA fail to yield the sperm, testicular biopsy/aspiration should be performed. Sperm recovery rates are improved with experience and a diagnostic PESA could be of value before a planned treatment cycle. Left-over epididymal sperm can be frozen for use in future cycles, avoiding the need for repeat surgery.

157

Effects of a permeation-enhanced testosterone transdermal system on prostate parameters in previously treated or untreated hypogonadal males

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Introduction: We evaluated the effects of a permeation-enhanced testosterone transdermal (TTD) system on prostate parameters in hypogonadal males who participated in two open-label, multicentre studies. Hormone levels, hypogonadal symptoms and sexual function were also assessed.

Patients and methods: Thirty-four previously treated (Study I) and 23 previously untreated (Study II) patients received TTD systems therapy for up to 6–12 months. Patients in Study I underwent 8 weeks of androgen withdrawal before starting TTD systems therapy. Systems were applied to back, abdomen, thighs or upper arms. Prostate volume (measured by TRUS) and PSA were assessed at 3, 6 and 12 months of TTD systems treatment; serum hormone levels were measured monthly. Hypogonadal symptoms were assessed by interviewing patients and sexual function was assessed by patient questionnaires (Watts, Davidson) and penile erectile function (RigiScan®) monitoring.

Results: Forty-five patients (29, Study I; 16, Study II) completed the trials. Mean morning serum testosterone (T) levels were normal in \geq 93% of patients. In Study I, the mean (SEM) prostate volume increased during treatment from the volume after 8 weeks of androgen withdrawal [14.1 (1.0) mL] to a volume of 17.5 (1.2) mL, similar to that during previous T replacement therapy, usually intramuscular (IM) T [16.6 (1.2) mL]. Prostate volume reached a maximum by treatment month 3 and then plateaued below the upper limit of normal (30 mL). In Study II, the prostate volume increased compared to hypogonadal baseline (HB) but remained within the normal range [17.8 (2.4) to 20.1 (2.2) mL]. PSA levels increased compared to HB [Study I, 0.5 (0.1) to 0.7 (0.1) ng/mL; Study II, 0.5 (0.1) to 0.8 (0.2) ng/mL] but not to previous IM T (Study I) and remained within normal limits (0–3.9 ng/mL). Hypogonadal symptoms and measures of sexual function improved. TTD systems were well tolerated; the most common adverse event was mild/moderate skin irritation.

Conclusion: TTD systems proved an effective modality for testosterone replacement in previously treated or untreated males with hypogonadism, and during the course of study were not associated with enlargement of the prostate beyond the normal reference range.

158

The role of orchidectomy in the management of postpubertal cryptorchidism

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Introduction: Studies of fertility in cryptorchidism based on testis biopsy and/or semen analysis confirm 40% of males with a history of cryptorchidism are subfertile, even if the opposite testicle has descended normally. However, post-pubertal males with unilateral cryptorchidism routinely undergo orchidectomy, because of the risk of future malignancy. We wished to challenge the concept whether routine orchidectomy is always justified in such cases.

Patients and methods: Fifty-four consecutive cases of post-pubertal cryptorchidism (51 unilateral and three bilateral) were analysed from 1984. Patients were aged from 15 to 66 years (mean 25.6). Six patients presented with primary infertility (unilateral, three, bilateral, three). The undescended testes were palpable in 36 (66%) cases. Fifty-three patients underwent a unilateral orchidectomy (24 with prosthesis insertion). One patient had a testis biopsy performed at orchidectomy.

Results: Torsion of an undescended testis (UDT) was found in two patients (4%). The location of the UDT was stated in 46 patients (superficial ring = 34; inguinal canal = 8, deep ring = 2, intra-abdominal = 2). Histology showed no active spermatogenesis in all testis specimens, including tubular atrophy ($n = 18$), Sertoli cell only ($n = 17$), maturation arrest ($n = 16$) and unstated ($n = 3$). Two patients (4%) had carcinoma *in situ* (aged 35 and 36 years). Sixteen patients (30%) had normal or hyperplastic Leydig cells, including one with a benign Leydig cell nodule.

Conclusions: This analysis of whole cryptorchid testis confirms that 1) cryptorchid testes cannot contribute to fertility, 2) have significant malignant potential, 3) may undergo torsion. Therefore, orchidectomy remains the treatment of choice for post-pubertal males presenting with unilateral cryptorchidism, and this is regardless of the fertility status.

159

Varicocele embolization versus ligation: venographic findings and causes of failure

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Introduction: Successful treatment of varicocele depends upon preventing venous reflux into the pampiniform plexus. This study reviews the results of internal spermatic vein embolization in a consecutive series of patients. Outcome was compared with that following ligation, and the reasons for treatment failure in men who required both ligation and embolization were examined.

Patients and methods: One hundred and forty-two patients, including 104 (73%) with infertility and 38 (27%) with symptomatic varicoceles were evaluated; 71 underwent venography with a view to embolization and 71 had ligation. Embolization was carried out with coils interposed with sclerosant (3% STD) and radiological findings were reviewed.

Results: Among the 71 men who underwent venography, embolization was technically impossible in 13 (18%), and ligation was subsequently carried out in 10. Failure was almost always associated with difficulty in cannulating an anomalous venous system and occasional venous spasm. In the 71 initially treated by ligation, the varicocele persisted or recurred in 14 (20%) and these were subsequently successfully embolized. Recurrence followed four radiologically successful embolizations: one of these underwent further venography which showed no reflux into the spermatic vein. Among 60 patients with subfertility who underwent semen analysis before and after treatment, sperm counts increased in 44 (73%) ($P < 0.01$) and six remained azoospermic.

Conclusion: Internal spermatic venography defines normal and anomalous venous anatomy, provides the opportunity for treatment by selective embolization and its immediate success may be objectively evaluated. Embolization is effective, straight-forward when associated with venous reflux from the renal vein and associated with minimal morbidity.

160

The World Health Organization varicocele trial

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Introduction: There is controversy about whether varicocele ligation will improve male fertility. Here we present the final data analysis of a WHO multicentre prospective randomized trial.

Patients and methods: The trial comprised 248 men with varicocele and poor semen quality whose female partner had normal tubal patency and ovulation. The men were randomized to immediate operation or an operation delayed for 1 year. Both groups were followed up to 12 months and the occurrence of pregnancy noted.

Results: Annual pregnancy rates were 31.3% (95% CI 23.0–40.0%) among couples allocated immediate operation and 14.4% (8.3–22.1%) among those allocated delayed operation ($P < 0.001$). There were improvements in semen quality after operation, not seen in the first year among men allocated to delayed operation. Clear biases in admission, randomization and follow-up occurred in some centres, but conclusions were similar when restricted to couples adequately randomized. Higher rates of non-compliance among couples allocated to delayed compared with immediate operation may also have biased the estimated impact of the operation on fertility prognosis.

Conclusions: In contrast to other recently published studies, the results suggest that varicocele treatment improves the prognosis of fertility and provides evidence that varicocele ligation is a useful treatment for male infertility.

161

There is significant sexual dysfunction following TURP

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Objectives: To quantify the incidence of sexual and orgasmic dysfunction in patients who have undergone TURP.

Patients and methods: Data were obtained on 4226 TURPs from the National Prostatectomy Audit.

Results: Forty percent of men were unhappy with their post-operative sexual function; 77% reported retrograde ejaculation and 52% described absent or altered orgasmic sensation. Although 26% of men reported a deterioration in erectile function after surgery, it is interesting that 20% of patients described an improvement. An important sub group were those men who were sexually active both before and after surgery ($n = 850$, mean age 71 years). Half of this cohort (408) reported sexual dissatisfaction after surgery. There was a strong association between retrograde ejaculation and orgasmic dysfunction.

	Normal orgasm	Impaired orgasm
Retrograde ejaculation	40% (340)	60% (510)
No retrograde ejaculation	84% (714)	16% (136)

$\chi^2 = 57$ $P < 0.001$

However, orgasmic dysfunction was even more strongly associated with post-operative sexual dissatisfaction.

Conclusions: When obtaining consent from patients for TURP the discussion concerning the high incidence of retrograde ejaculation should include the additional likelihood of altered orgasmic sensation. Furthermore, for those patients who wish to retain sexual activity

after surgery, the qualitative aspects of sexual dysfunction in potent men should be seriously considered. Half of these men can expect to experience sexual dissatisfaction following surgery.

162

Distal penile fibrosis following intracavernosal prostaglandin E1 injections

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Introduction: Intracavernosal injections with papavarine and phentolamine are associated with fibrosis of the tunica albuginea or corpus cavernosum, with a reported incidence after one year of injections ranging from 1.5 to 57%. Recently, prostaglandin E1 (PGE1) has superseded these agents, although the long-term incidence of fibrosis with its use is not well documented.

Patients and methods: Forty patients (median age 60 years) on a programme of intracavernosal self-injection with PGE1, were followed for a minimum of 2 years. They had a mixed aetiology of erectile dysfunction. Fibrotic changes were detected by careful palpation of the penis and confirmation sought with ultrasonography of the penile shaft.

Results: The dose of PGE1 injected varied between 15 and 60 µg. All patients achieved grade 4 erections for 45 to 60 min. The number of injections received before the onset of fibrosis varied from 20 over a period of 6 months to a maximum of 46 over one year. Four cases (10%) of penile Peyronie-like fibrosis were diagnosed clinically. In all cases, the fibrosis occurred distal to the site of injections and not at the site of injection. The fibrosis resolved completely within 6 months of withdrawal of treatment and appeared to be independent of the age of the patient and dose of PGE1.

Conclusions: Peyronie-like fibrosis of the penis, distal to the injection site, is a significant complication following PGE1 intracavernosal therapy. The high incidence and the unknown aetiology of this complication emphasizes the importance of careful follow-up. The possible pathological processes involved will be discussed.

163

Alterations in endothelin B receptor-binding sites on the cavernosal tissue of diabetic rabbits

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Objectives: To investigate the density and distribution of endothelin-1 (ET-1) and endothelin receptor subtypes in rabbit cavernosal tissue and to assess any changes brought about by the onset of diabetes mellitus (DM).

Materials and methods: Hyperglycaemic non-ketotic DM was induced in New Zealand white rabbits using alloxan. The penises were excised from the diabetic rabbits three months ($n = 6$) and six months ($n = 6$) after the induction of DM and stored at -70°C . Transverse serial sections ($10\ \mu\text{m}$) were cut using a cryostat and thaw-mounted on to gelatinized microscope slides. Low and high resolution autoradiographs were taken using radioligands for ET-1, endothelin A (ET_A) and endothelin B (ET_B) receptors and the autoradiographs analysed densitometrically. The results were compared with those from six age-matched healthy control rabbits. Immunohistochemical localization of ET-1 immunoreactivity was also performed on $10\ \mu\text{m}$ sections using the avidin-biotin peroxidase complex technique.

Results: ET-1, ET_A and ET_B receptor binding sites were primarily localized to the smooth muscle cells of the corpus cavernosum and the endothelium lining the cavernosal spaces. A significant ($P < 0.02$) increase in ET_B receptor binding sites (median $4.7\ \text{d.p.m.} \times 1000/\text{mm}^2$, range $2.9\text{--}14.5\ \text{d.p.m.} \times 1000/\text{mm}^2$, $n = 6$) was found only in cavernosal tissue 6 months after induction of DM when com-

pared to age-matched healthy controls ($1.4, 1.0\text{--}4.6$, $n = 6$). ET-1 immunoreactivity was also localized to the cavernosal smooth muscle and endothelium lining the spaces.

Conclusions: ET_B receptor binding sites are significantly increased in rabbit cavernosal tissue 6 months after the induction of DM. This alteration may represent a pathophysiological pathway in diabetic erectile dysfunction or a compensatory response to the impaired nitric oxide release which has been reported in diabetic animal models and humans.

164

Should we offer inflatable penile prosthesis to all patients?: a comparative review of 104 patients with malleable or inflatable prostheses

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Introduction: During the period 1987–1995, 104 patients had a penile prosthesis inserted, mainly to treat impotence. In view of the higher cost of inflatable prosthesis we wished to assess the success and satisfaction rate of both types of prosthesis.

Patients and methods: The case notes of 104 patients were reviewed and questionnaires sent enquiring about usage of the prosthesis and the satisfaction of the patient and partner.

Results:

	Inflatable (multipart)		Malleable	
Total patients/ (procedures)	66	(77)	38	(48)
Mechanical problems	5	6.4%	1	2.1%
Replacement	1	1.3%	5	10.8%
Infection				
Primary	2	6.4%	0	43.3%
Revisions	3		2	
Costing	£5000		£1500	

Mechanical failures included tube leaks and a case of ruptured cylinders (twice) in a patient, due to a pointed bicycle seat. Five malleable devices were replaced: one for incorrect positioning in another centre, difficulty in concealment, inadequate length/dislike of the prosthesis and a fractured prosthesis.

Conclusion: This preliminary review of the results indicates a high level of satisfaction (90%) by both patients and their partners, more so with the inflatable device as concealment is a problem with the malleable prosthesis. Detailed analysis of the questionnaire will be presented. Despite the higher cost of inflatable prostheses it should be offered to men aged under 60 years as it is more pleasing.

165

Late recurrence of germ cell cancer: the need for more active surveillance and early surgery

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Introduction: Current practice for germ cell cancer involves stopping CT surveillance after 2 years providing the findings of CT are normal. A recent report by Fossa *et al.* (J Clin Oncol 1992 10:569–73) using elective retroperitoneal lymph-node surgery (RPLND) after a chemotherapy-induced CT scan had confirmed complete remission, has shown that 22/78 (28%) had small areas of residual mature teratoma. To assess the risk of leaving these microscopic foci, a review has been undertaken on patients treated in this unit.

Patients and methods: A series of 256 patients with metastatic germ cell cancer treated between January 1978 and December 1994 were reviewed. Node dissection was only used if macroscopic disease was visible on CT at completion of treatment. The median follow-up was 68 months and 71 patients were followed for more than 10 years.

Results: Of 201 treated with chemotherapy alone, 50 (25%) relapsed before 18 months and five (3%) of the 151 survivors at 18 months relapsed subsequently at 23, 34, 52, 111 and 130 months; 55 patients underwent RPLND for residual mass after chemotherapy. Five (9%) relapsed before 18 months and two (4%) of the 18-month survivors subsequently relapsed at 38 and 69 months. Of the seven late relapses, two have died of chemotherapy-resistant tumour, five others failed second-line chemotherapy and two remained disease free for 2 and 72 months, while two of the remaining three have progressive disease and one static retrocrural nodes.

Conclusions: As the late relapse rate of 4% is substantially less than the incidence of mature teratoma from the elective RPLND series after chemotherapy, and surgery is emerging as treatment of choice for such late relapses, there is a need for increased vigilance of surveillance that will need to include ultrasonography and/or CT and extend beyond 20 years.

166

The critical role of surgery following chemotherapy for para-aortic nodal masses in non-seminomatous germ-cell tumours

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Introduction: Para-aortic masses are removed after chemotherapy for metastatic non-seminomatous germ cell tumours of testis to excise possible persistent tumour and to define its histological content. If undifferentiated tumour is present, further chemotherapy may be recommended; this study was performed to determine whether this is necessary.

Patients and methods: Amongst 328 men who had post-chemotherapy para-aortic lymphadenectomy since January 1979, 65 (20%) had undifferentiated tumour in the excised specimen. Prognostic factors have been examined which may have had an influence on survival and local control of abdominal disease.

Results: The completeness of surgical excision was highly predictive for survival. Other factors, including markers at surgery, difficulty of surgery, initial stage, site and size of tumour mass and type of initial chemotherapy, were relatively unimportant. Survival was not improved by post-operative chemotherapy in the group of 42 patients

who had complete excision (although there could have been some bias in this analysis); 60% were alive at 5 years with follow-up extending to 16 years (median interval 4 years).

Conclusion: Additional chemotherapy is not essential after complete excision of residual masses which contain undifferentiated teratoma.

167

When contralateral testis biopsy is essential in testicular cancer

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Introduction: Carcinoma *in situ* (CIS) of the testis accurately predicts the development of an invasive tumour. Although this condition is present in the contralateral testis in 5% of patients with testicular cancer, very few surgeons in the UK perform a contralateral testicular biopsy routinely.

Patients and methods: To identify a high risk group, 205 patients with testis cancer, said to be at increased risk because of testicular atrophy (volume ≤ 12 mL) or a history of maldescent, underwent biopsy. In addition semen analyses and endocrine profiles were performed.

Results: CIS was found in 21 (13%) of 156 cases where histological review was carried out. The prevalence of CIS was not related to the type of biopsy (open/needle), the diagnosis of the established tumour (seminoma/non-seminoma), gonadotrophin or sex hormone levels. Testicular maldescent alone, testicular atrophy and a combination of both conditions was associated with CIS in 1/58 (2%), 12/55 (22%) and 8/37 (22%) cases, respectively. A sperm density of less than 10×10^6 /mL was associated with CIS in 16/81 (20%) cases compared to 0/27 cases when the density was greater than this value. Patients whose tumour presented by the age of 30 had CIS in 17/72 (24%) cases compared to 4/81 (5%) of the older group ($P = 0.001$). When testicular atrophy was found in patients in the younger group the prevalence of CIS was 16/42 (38%).

Conclusion: Contralateral testicular CIS is closely associated with a testicular volume of < 12 mL but not with a history of maldescent when the volume is greater than this. Biopsy is strongly recommended in this high-risk group and the description of a patient with a testicular lump should include the size of the contralateral testis.